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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,447	02/13/2004	Chandra Vargeese	MBHB02-312-G (600.041)	2130

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MCDONNELL, BOEHNEN, HULBERT AND BERGHOFF, LLP
300 SOUTH WACKER DRIVE
SUITE 3100
CHICAGO, IL 60606

EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/780,447	VARGEESE ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,6,15,16,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5, 6, 15, 16, 20, and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted May 14, 2007 wherein claims 5, 6, 20, and 21 are amended and claims 1-4, 7-14, and 17-19 are cancelled, and the abstract of the specification is amended to better represent the claimed invention. This application is a continuation in part of 10/427160, currently pending, filed April 30, 2003, currently pending, which is a continuation in part of PCT/US02/15876, filed May 17, 2002, which claims benefit of provisional applications: 60/292217, filed May 18, 2001, 60/306883, filed July 20, 2001, 60/311865, filed August 13, 2001, and 60/362016, filed March 6, 2002. This application is also a continuation-in-part of PCT/US03/05346, filed February 20, 2003, and PCT/US03/05028, filed February 20, 2003, which claims benefit of the following provisional applications: 60/358580, filed February 20, 2002, 60/363124, filed March 11, 2002, 60/386782, filed June 6, 2002, 60/406784, filed August 29, 2002, 60/408378, filed September 5, 2002, 60/409293, filed September 9, 2002, and 60/440129, filed January 15, 2003.

However, the above priority documents PCT/US02/15876, filed May 17, 2002, 60/292217, filed May 18, 2001, 60/306883, filed July 20, 2001, 60/311865, filed August 13, 2001, 60/362016, filed March 6, 2002, PCT/US03/05346, filed February 20, 2003, PCT/US03/05028, filed February 20, 2003, 60/358580, filed February 20, 2002, 60/363124, filed March 11, 2002, 60/386782, filed June 6, 2002, 60/406784, filed August 29, 2002, 60/408378, filed September 5, 2002, 60/409293, filed September 9, 2002, and 60/440129, filed January 15, 2003, upon which priority is claimed fail to provide adequate support under 35 USC 112, first paragraph for the claimed subject

matter of instant claims 5, 6, 15, 16, 20, and 21 of this application because these provisional applications are not seen to disclose any conjugates comprising a galactosamine cluster glycoside moiety. Thus, the filing date of the instant claims is deemed to be the filing date of the parent application 10/427160, April 30, 2002. If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Claims 5, 6, 15, 16, 20, and 21 are pending in this application.

Claims 5, 6, 15, 16, 20, and 21 as amended are examined on the merits herein.

Applicant's amendment, submitted May 14, 2007, with respect to the objection to the abstract for misrepresenting the claimed invention has been fully considered and found to be persuasive to remove the rejection as the abstract as amended recites only galactosamine and N-acetyl galactosamine conjugates of the active molecules.

Applicant's amendment, submitted May 14, 2007, with respect to the objection to instant claims 20 and 21 for a typographical error, has been fully considered and found to be persuasive to remove the objection as the claims have been amended to correct the error. Therefore the objection is withdrawn.

Applicant's amendment, submitted May 14, 2007, with respect to the rejection of instant claims 5-6, 10-11, 15-16, and 20-21 under 35 USC 112, first paragraph, for lacking enablement for the full scope of biologically active molecules, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to recite only small interfering RNAs. Therefore the rejection is withdrawn.

Applicant's amendment, submitted May 14, 2007, with respect to the rejection of instant claims 5-6 and 15-16 under 35 USC 103 for being anticipated by Low et al. in view of Connolly et al., of record in the previous action, has been fully considered and found to be persuasive to remove the rejection as the references do not disclose small interfering RNAs. Therefore the rejection is withdrawn.

The following grounds of rejection of record in the previous action are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-6, 15-16, and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Low et al. (PCT international publication WO90/12096, of record in previous action) in view of Connolly et al. (Reference included with PTO-1449, of record

in previous action) further in view of Li et al. (PCT international publication WO00/44914, of record in previous action) Low et al. discloses that exogenous molecules conjugated to a biotin or folate ligand exhibit improved transport across the cell membrane. (p. 7, lines 5-24) This process takes place through the receptor mediated transmembrane transport of the biotin or folate moiety of the complex. (p. 4, lines 26-30) Various biologically active molecules may be transported in this manner. (pp. 9-11) The method is recognized as being particularly useful for the transport of polynucleotides across the cell membrane. (p. 6, lines 16-20) The complexes are typically formed by covalently attaching the exogenous molecule to the receptor-activating moiety by any common linker. (p. 12, lines 1-25) Low et al. does not specifically disclose the compounds of instant claims 5-6 and 15-16 in which the targeting moiety is a tris(N-acetylgalactosamine) cluster glycoside and the biologically active molecule is a short interfering RNA.

Connolly et al. discloses that synthetic cluster glycosides containing three N-acetylgalactosamine ligands (p. 940, diagram 1, bottom of page) bind to cell surface receptors on rabbit hepatocytes and are taken up into the cells by endocytosis. (p. 939, right column, third paragraph)

Li et al. discloses a double-stranded RNA which acts to specifically inhibit expression of a target gene. (p. 9, lines 13-24, p. 11, lines 20 – p. 12, line 10) One embodiment of this invention is a double-stranded RNA which inhibits expression of a gene required for maintenance of a cancer phenotype, therefore inhibiting cancer cells. (p. 16, lines 24-31) This dsRNA is reasonably considered to be a siNA molecule

according to instant claims 7-9 and 17-19, and also an exogenous molecule according to Low et al. The dsRNA can be delivered to a cell by a variety of different methods. (p. 14, lines 10-29)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a conjugate comprising a biologically active molecule conjugated to a cluster of three N-acetylgalactosamine residues by the trivalent linkers of formulas 119 and 121, attached with the linkers of instant claims 15-16. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the compounds of Low et al. in view of Connolly et al. by attaching the dsRNA molecules of Li et al. by the sense strand, as the exogenous molecule described by Low et al. One of ordinary skill in the art would have been motivated to make this modification because Low et al. discloses that conjugation of a biologically active molecule to a molecule which undergoes transport across the cell membrane improves the uptake of the biologically active molecule into its target cells, and because Connolly et al. discloses that a trivalent cluster glycoside of similar structure to the claimed compounds is taken up specifically by hepatocytes, making it a useful targeting moiety for delivery of biologically active compounds to the liver. One of ordinary skill in the art would have been motivated to attach a dsRNA according to Li et al. as the biologically active molecule in order to improve its delivery into the target cell for therapeutic gene inhibition, because Low et al. discloses that various polynucleotides can be delivered to cells by conjugation to a moiety that gets taken up into the cell. One of ordinary skill in the art would reasonably have expected success because the selection of particular

linking groups to conjugate two known molecules is well within the ordinary and routine level of skill in the art, and because the conjugates of Low et al. are already disclosed to be useful for the delivery of nucleic acids.

Applicant cannot rely on the priority documents PCT/US02/15876, 60/292217, 60/306883, 60/311865, 60/362016, PCT/US03/05346, PCT/US03/05028, 60/358580, 60/363124, 60/386782, 60/406784, 60/408378, 60/409293, and 60/440129 to overcome this rejection because these applications do not provide adequate written description for the claimed invention as discussed above. Specifically, these provisional applications do not describe galactosamine-conjugated nucleic acids or otherwise indicate that galactosamine or N-acetylgalactosamine may be conjugated to a nucleic acid to improve its pharmacokinetic properties.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted May 14, with respect to the above ground of rejection has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that neither Low et al. nor Connolly et al. enables a conjugate containing a siRNA as required by the amended claims. However, this argument ignores the additional disclosure of Li et al. which discloses and enables inhibitory dsRNAs that are reasonably considered to be siRNAs according to the claimed invention. Furthermore, according to MPEP 2145, One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the instant case, consideration of all three references in combination would enable one of ordinary skill in the art to attach a small inhibitory RNA to an N-acetylgalactosaimne cluster glycoside according to Connolly et al. by an appropriate linker, with a reasonable expectation that such a molecule would be taken up by hepatocytes at an improved rate compared with the unmodified siRNA molecule.

Applicant also argues that at the time of invention, different types of RNAs were understood to have such different structures and mechanisms of action that one of ordinary skill in the art would not have been able to predict the efficacy of a siRNA conjugate of the instant claims. However, contrary to Applicant's assertion, Low et al. discloses that a wide variety of different single and double stranded nucleic acids of various lengths including antisense oligonucleotides and other small nucleotides capable of regulating gene transcription and translation, can all be enhanced in their transmembrane transport by being conjugated to a molecule that is naturally taken up into a cell. Therefore one of ordinary skill in the art would have reasonably expected that the same strategy would work for small inhibitory RNAs.

Therefore the rejection is deemed proper and made **FINAL**.

Conclusion

No claims are allowed in this application. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric Olson
Patent Examiner
AU 1623
7/5/07

Anna Jiang
Supervisory Patent Examiner
AU 1623